Remarks

Responsive to the Office Action dated November 18, 2003, Applicants request entry of the above amendments and consideration of the following remarks. A reconsideration of the present application respectfully is requested. Claims 10-11 and 17-20 have been canceled. As such, claims 1-9 and 12-16 are pending and under consideration. Each of these claims is believed to be in condition for allowance and such favorable action is requested.

§112 Rejections

Claims 1-9 and 12-16 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claims 1 and 12 have been rejected as being vague and indefinite as it is not clear how the methods will distinguish irritable bowel syndrome (IBS) from inflammatory bowel disease. With respect to claim 1, the preamble of the claim has been amended to state that it is a method for precluding the diagnoses of irritable bowel syndrome and other non-inflammatory etiologies. As such, claim 1 clearly sets forth a clear resolution step that relates to the preamble. With respect to claim 12, the preamble of the claim has been amended to state that it is a diagnostic assay for determining whether a sample contains an elevated level of endogenous lactoferrin as compared to a reference value for healthy control subjects. As such, claim 12 clearly sets forth a clear resolution step that relates to the preamble. Applicants request withdrawal of this 112 rejection to claims 1 and 12.

Claims 1 and 12 have also been rejected as being vague and indefinite because it is not clear as to what interaction the sample and the antibodies to human lactoferrin will produce. Applicants respectfully submit that as amended claims 1 and 12 are not indefinite.

With respect to claim 1, it is clear that if a sample contains an elevated level of lactoferrin, diagnoses of IBS or other noninflammatory etiologies are substantially precluded. As stated on page 8, lines 11-14 of the specification, "a diagnosis of active IBD cannot be established solely on the basis of a positive result with the assay of the present invention. However, a positive result with the assay of the present invention will permit the substantial preclusion of a diagnosis of IBS or other noninflammatory etiologies." As such, claim 1 is not vague and indefinite. By using the method of claim 1, if the sample does not contain an elevated level of lactoferrin, IBS and other noninflammatory etiologies are precluded.

With respect to claim 12, the assay determines whether the enzyme-linked antibody bound sample has an elevated level of endogenous lactoferrin as compared to a reference value for healthy control subjects. Applicants submit that determining whether a bound sample has an elevated level of lactoferrin as compared to a reference value is not vague and indefinite. As such, Applicants request withdrawal of the 112 rejections of claims 1 and 12.

Claims 4 and 16 have been rejected as being indefinite for being in improper Markush format. Applicants have amended claims 4 and 16 in accordance with the Examiner's suggestions and request withdrawal of the rejection as to these claims.

Claims 6-9 and 12-14 have been rejected for the use of the terms "treated sample" and "readable sample." Applicants have amended the claims in accordance with the Examiner's suggests to provide clarity. As such, Applicants request withdrawal of the 112 rejections of these claims.

Claims 7 and 12 have been rejected as being indefinite because it is not clear as to what the term "enzyme-linked polyclonal antibody" encompasses. Claims 7 and 12 have

been amended to state that the enzyme-linked polyclonal antibodies are allowed to bind to capture lactoferrin. As such, Applicants submit that the claim is clear and request withdrawal of the 112 rejections of these claims.

103 Rejections

Claims 1-2 and 4-7 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,124,252 to Guerrant et al (the "Guerrant reference") in view of the article by Peen et al. (Gut, 1996, 38, 135-140) (the "1996 Peen reference") and in further view of Sugi et al. (The American Journal of Gastroenterology, Vol. 91, No. 5, 927-934, 1996) (the "Sugi reference"). As the combination of the Guerrant reference in view of the 1996 Peen reference in further view of the Sugi reference neither teaches nor suggests a method for precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies if a sample does not contain an elevated level of endogenous lactoferrin, Applicants traverse the rejection.

Amended independent claim 1 recites a method for substantially precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies by determining that a fecal sample does not contain an elevated level of endogenous lactoferrin. The Guerrant reference, on the other hand, teaches an in vitro test for determining the presence of leukocytes in a fecal sample, which is sensitive to the numbers of fecal leukocytes typically found in inflammatory diarrhea specimens, by testing the fecal sample with an assay utilizing an antibody for lactoferrin. The in vitro test used in the Guerrant reference merely states that a fecal sample is tested and observed for the presence of lactoferrin. The test is sensitive to the numbers of fecal leukocytes that can typically be found in inflammatory diarrheal specimens. This test is not sensitive enough to preclude a diagnosis of IBS by determining that a fecal

sample does not contain elevated levels of lactoferrin. It is merely a diagnostic clue that a fecal sample tested may be inflammatory diarrhea.

The 1996 Peen reference also does not teach or suggest substantially precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin. Rather, the 1996 Peen reference teaches an analysis of the distribution of hsp-65 and lactoferrin in biopsy specimens from patients with inflammatory bowel disease and primary sclerosing cholangitis. The 1996 Peen reference in no way suggests that diagnosis of IBS and other non-inflammatory etiologies can be precluded because a fecal sample does not contain an elevated level of endogenous lactoferrin.

The Sugi reference also does not teach or suggest substantially precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin. The Sugi reference merely teaches using fecal lactoferrin as a marker for disease activity in inflammatory bowel disease. The Sugi reference, like the Guerrant reference and the 1996 reference, in no way suggests that if a fecal sample does not contain an elevated level of endogenous lactoferrin that diagnoses of irritable bowel syndrome and other noninflammatory etiologies may be precluded.

As the Guerrant reference, 1996 Peen reference and Sugi reference neither teach or suggest a method for substantially precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin, Applicants request withdrawal of the 103(a) rejection

of claim 1. As claims 2 and 4-7 depend directly or indirectly from claim 1, Applicants request withdrawal of the rejection of these claims as well.

Claims 3, 8-9 and 12-16 have been rejected under 35 U.S.C. 103 (a) as being unpatentable over the Guerrant reference in view of the 1996 Peen reference and in further view of the Sugi reference and in further view of Peen et al. (Gut, 1993, 34, 56-62) (the "1993 Peen reference"). With respect to claims 3 and 8-9, as stated about neither the Guerrant reference, the 1996 Peen reference nor the Sugi reference teach or suggest substantially precluding diagnoses of irritable bowel syndrome and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin as claimed by independent claim 1.

The 1993 Peen reference also does not teach or suggest substantially precluding a diagnosis of IBS and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin. Rather the 1993 Peen reference teaches high frequencies of IgG anti-lactoferrin antibodies in serum samples from patients with ulcerative colitis and primary sclerosing chloangitis. There is no teaching or suggestion that diagnoses of IBS and other noninflammatory etiologies can be precluded because a fecal sample does not contain an elevated level of lactoferrin.

As neither the Guerrant reference, the 1996 Peen reference, the Sugi reference nor the 1993 Peen reference teach or suggest substantially precluding a diagnosis of IBS and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin, Applicants request withdrawal of the rejection of claims 3 and 8-9 as they depend directly or indirectly from independent claim 1.

With reference to claims 12-16, independent claim 12 is drawn to an assay determining whether an enzyme-linked antibody bound sample contains an elevated level of lactoferrin as compared to a reference value for health control subjects, wherein the optical density of the enzyme-linked antibody bound sample is read at 450 nm. As the Guerrant reference, the 1996 Peen reference, the Sugi reference nor the 1993 Peen reference neither teach nor suggest a diagnostic assay for determining whether a fecal sample contains an elevated level of endogenous lactoferrin as compared to a reference value for healthy control subjects by determining the optical density of an enzyme-linked antibody bound sample at 450 nm, Applicants traverse the rejection.

The Guerrant reference teaches an in vitro test for determining the presence of leukocytes in a fecal sample that is sensitive to the numbers of fecal leukocytes typically found in inflammatory diarrheal specimens, by testing the fecal sample with an assay utilizing an antibody for lactoferrin. The Guerrant reference does not teach or suggest determining the optical density of an enzyme-linked antibody bound sample at 450 nm. Further, the Guerrant reference does not even teach or suggest determining the optical density of a sample.

The 1996 Peen reference also does not teach or suggest determining the optical density of an enzyme-linked antibody bound sample at 450 nm. Rather, the 1996 Peen reference teaches an analysis of the distribution of hsp-65 and lactoferrin in biopsy specimens from patients with inflammatory bowel disease and primary sclerosing cholangitis. There is no discussion of determining the optical density of an enzyme-linked antibody sample at 450 nm or determining the optical density of a sample.

The Sugi reference also does not teach or suggest determining the optical density of an enzyme-linked antibody bound sample at 450 nm. Rather, the Sugi reference

teaches measurement of fecal lactoferrin. The Sugi reference teaches an enzyme reaction test and measurement of color development with a microplate colorimeter at 510/630 nm, and not 450 nm. The measurement of optical density of an enzyme-linked antibody bound sample at 450 nm is important to determine if the fecal sample contains an elevated level of endogenous lactoferrin and if so, substantially precluding a diagnosis of irritable bowel syndrome.

The 1993 Peen reference also does not teach or suggest measurement of optical density of an enzyme-linked antibody bound sample at 450 nm. The 1993 Peen reference teaches high frequencies of IgG anti-lactoferrin antibodies in serum samples from patients with ulcerative colitis and primary sclerosing chloangitis. The 1993 Peen reference differs from independent claim 12 in that it detects IgG anti-lactoferrin antibodies in serum samples and not fecal samples as claimed by claim 12 of the present application. Furthermore, the 1993 Peen reference reads the optical density of positive reference at 405 nm. Again, it is important to read the optical density of an enzyme-linked antibody bound sample at 450 nm to determine if the fecal sample contains an elevated level of endogenous lactoferrin and if so, being able to substantially preclude a diagnosis of irritable bowel syndrome.

As the Guerrant reference, the 1996 Peen reference, the Sugi reference nor the 1993 Peen reference neither teach nor suggest a diagnostic assay for determining whether a fecal sample contains an elevated level of endogenous lactoferrin as compared to a reference value for healthy control subjects by determining the optical density of an enzyme-linked antibody bound sample at 450 nm, Applicants request withdrawal of the 103(a) rejection of claim 12. As claims 13-16 depend directly or indirectly from claim 12, Applicants request withdrawal of the 103(a) rejection as to these claims as well.

The present application is believed to be in condition for allowance, and Applicants request that a timely notice of allowance be issued for this case. Should any unresolved issues remain in the case, please feel free to contact the undersigned at the phone number listed below.

Respectfully submitted.

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